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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/039,645	10/25/2001	Alan S. Kopin	00398/510002	9279

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EXAMINER
BERTOGLIO, VALARIE E

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/17/2003 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/039,645	Applicant(s) KOPIN ET AL.	
	Examiner Valarie Bertoglio	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **The sequence listing discloses that all SEQ ID Numbers correspond to the species Homo sapiens. This is inconsistent with the text of the specification. For example, SEQ ID NO:1 corresponds to the rat mu opioid receptor and therefore should not list Homo sapiens in the sequence listing.** Applicants must file a "Sequence Listing" accompanied by directions to enter the listing into the specification as an amendment. Applicant also must provide statements regarding sameness and new matter with regards to the CRF and the "Sequence Listing."

Failure to fully comply with the sequence rules in response to the instant office action will be considered non-responsive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is directed to a method for treating, reducing or preventing pain in a mammal, comprising administering to said mammal a nucleic acid encoding a constitutively active (claims1-12) or hypersensitive (claim 13) mu opioid receptor under the control of an inducible promoter (claim 5), a constitutive promoter (claim 6), or a tissue specific promoter (claim 7). In particular, the nucleic acid has a single Asn to Ala point mutation at amino acid 150 of SEQ ID NO:1 (claims 2 and 3). In a further embodiment, the pain treated is back pain (claim 3). Claims 14-25 are directed to a therapeutic composition comprising a nucleic acid encoding a

constitutively active (14-24) or hypersensitive (claim 25) mu opioid receptor. Claims 26-33 are directed to kits comprising the same nucleic acid. The only intended use for the products of claims 14-33 is in gene therapy as encompassed by claims 1-13.

The specification teaches that single Asn to Ala point mutation at amino acid 150 of SEQ ID NO:1 renders the rat mu opioid receptor constitutively active and hypersensitive *in vitro*, i.e. it is active in the absence of an agonist and has a higher affinity for agonists. However, *in vitro* function of an expression vector does not provide a prediction of therapy for any pain condition as the results only pertain to constitutive activation of the mu opioid receptor in HEK293 cells. The specification fails to provide a correlation to therapeutic levels of expression of a nucleic acid encoding a constitutively active or hypersensitive mu opioid receptor in an in vivo setting in any subject having pain. The specification points out that the examples and guidance set forth in the specification pertains to in vitro use of nucleic acid but states that the results are transferable to any mammal of interest (paragraph bridging pages 50-51).

The nature of the invention being gene therapy, the state of the prior art is not well developed and is highly unpredictable. In general, *in vitro* gene expression is not representative of gene expression in a host animal whose cells have been somatically transfected *in vivo*. Verma (1997, Nature, Vol. 389, pages 239-242) states that out of the more than 200 clinical trials currently underway, no single outcome can be pointed to as a success story (page 239, col. 1). Numerous factors that have not been overcome by routine experimentation complicate the art of gene therapy. Eck and Wilson explain that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the

protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all factors that differ dramatically based on the vector used, the protein being produced, and the disease being treated (Eck and Wilson, 1996, 'Gene-Based Therapy' in The Pharmacological Basis of Therapeutics, paragraph bridging pages 81-82). Verma states that one major obstacle to success has been the inability to deliver genes efficiently and obtain sustained expression (page 239, column 3). It is further noted that Eck and Wilson support the importance of tailoring a gene therapy vector and methods to specific diseases and disorders (see page 82, column 1, 1st paragraph). Accordingly, Miller (1995, FASEB J., Vol. 9, pages 190-199) states that effective vectors will vary according to whether expression of the target gene in non-target cells will be toxic and to whether they are capable of transfecting target cells.

The state of the art to gene therapy, specifically with respect and pain control, was that, as with other forms of gene therapy, the efficacy depends on many factors, mainly the vector and route of administration (Iadarola, 1997, *Molecular Neurobiology of Pain*, Vol. 9, page 353-354, Discussion 1st and 2nd paragraphs). Iadarola teaches that the promoter used to drive expression of the target gene can vary the level and duration of expression (page 355, 1st full paragraph) and concludes that while several potential routes of gene therapy administration exist, each has its own set of advantages and constraints (page 356, last paragraph).

The instant specification does not provide any *in vivo* working examples and teaches only prophetically how one might treat pain using a nucleic acid encoding constitutively active or hypersensitive mu opioid receptor. The specification does not teach how to construct an effective therapeutic viral or non-viral vector, which cells types are effectively targeted by which vector, how to deliver a given vector such that it reaches targeted cells, or that any therapeutic level of expression could be achieved to effect a therapeutic response to any particular type of pain, in any particular tissue. The specification merely proposes several potential methods of

transfection that are known in the art using a variety of potential vectors to treat any type of pain, and specifically back pain. It does not demonstrate, by practice, the in vivo transfection of any type of cell with nucleic acid encoding the mutant receptors operably linked to any promoter, the in vivo expression of said transformed nucleic acids, or the levels of expression and function of the mutant mu opioid receptors necessary to achieve inhibition or treatment of pain (for example, see paragraph bridging pages 38 and 39; pages 52 and 53). As such, with respect to the unpredictable nature of the gene therapy art, and particularly when taken with the specification's lack of any teaching of or sufficient guidance for constitutively active or hypersensitive mu opioid receptor *in vivo,* it is not predictable if the mutant opioid receptor gene expression would start or continue in target cells or in any cells at levels and for a duration which would be considered therapeutic in a subject experiencing pain since somatic gene delivery often results in only limited expression in an adequate number of cells.

It is of further interest to note that Wang et al. (1994, Life Sciences, Vol. 54, pages 339-350) and Sadee et al. (1994, Analgesia, Vol. 1, pages 11-14) teach that agonist stimulation causes a gradual constitutive mu opioid receptor activation wherein the receptor no longer requires an agonist for signal transduction and that it is this increasingly constitutive state that is linked to increased opioid dependence. This finding raises the question of whether adding a constitutively active mu-opioid receptor via gene therapy would result in adverse effects including drug tolerance and withdrawal. As stated above, it cannot be predicted how long and how much constitutively active mu opioid receptor would be present in a cell if administered by gene therapy. Would the therapy result in dependence, agonist tolerance, or withdrawal, especially once levels of constitutively active protein declined?

Accordingly, in view of the quantity of experimentation necessary to determine the parameters listed above for achieving constitutively active mu opioid gene therapy, the lack of

direction or guidance provided by the specification to carry out constitutively active mu opioid gene therapy as broadly claimed, the absence of working examples for the demonstration or correlation to achieving therapeutic levels of constitutively active or hypersensitive mu opioid receptor, and the breadth of the claims, and the unpredictable and undeveloped state of the art with respect to gene therapy, it would have required undue experimentation for one skilled in the art to make and use the claimed invention with a reasonable expectation of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of the term "sufficient" in claim 1 are unclear. The specification defines the phrase "disease-inhibiting amount" (page 11, lines 7-14) in vague and unclear terms and does not address what an "amount sufficient to treat" is.

The phrase "human equivalent" in claim 3 is unclear. It is unclear if there is a human equivalent of the Asn to Ala mutation or if the phrase is referring to the human gene equivalent to that of SEQ ID NO:1.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Mansour (1997, Journal of Neurochemistry, Vol. 68, pages 344-353) describe the hypersensitive nature of the Asn to Ala mutation at amino acid 150 in the mu opioid receptor. However, Mansour does not disclose using the mutant receptor as a therapeutic composition and thus, was not relied upon in the instant application.

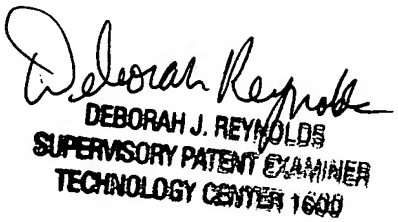
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Valarie Bertoglio
Patent Examiner



Application No.: 10/039645

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: the Sequence listing discloses that all sequences correspond to the species homo sapiens. This is inconsistent with the specification. For example, SEQ ID NO:1 corresponds to the rat mu opioid receptor.

If Necessary, Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE